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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,321	KALLIES ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 30-47* is/are rejected.

7)☒ Claim(s) *17-19,26,27 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/28/2007; 10/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of the invention of Group I, drawn to a genetically modified cell or non-human organism comprising a modified *blimp* gene, in the reply filed on 06/04/2008 is acknowledged. In the same reply, Applicant elected the species of functional Blimp and B cells. The traversal is on the ground(s) that a requirement for restriction entails an analysis of the subject application in light of the roles governing this practice, i.e., 37 C.F.R. §1.499 and PCT Rules 13.1 and 13.2. Applicant points out that PCT Rule 13.1, first sentence, states: "The international application shall relate to one invention only or to a group of inventions so linked as to form a single, general inventive concept ('requirement of unity of invention'), while PCT Rule 13.2 states: "The expression "technical features' shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art". Applicant submits that Groups II-IV represent methods of using the product of Group I. Specifically, the method of phenotyping a cell of the hematopoietic system, i.e., the subject matter of Group II, is based on screening a genetically modified hematopoietic cell or a genetically modified animal (product of Group I) for activity of the reporter gene. The method for testing the antigenicity or immunogenicity of a vaccine, i.e., the subject matter of Group III, is based on administering the vaccine to a genetically modified hematopoietic cell or a genetically modified animal (product of Group I) and testing for the presence of the reporter

molecule. The method of screening for agonists or antagonists of terminal differentiation of hematopoietic cells (Group IV) is based on exposing a genetically modified hematopoietic cell or a genetically modified animal (Group I) to a candidate agent and testing for the presence or change in the level of the reporter molecule. Therefore, Group I and Groups II-IV are related to each other as product and process of use, which falls within the allowed combination of claims. See Item 2) on page 3 of the Office Action. Applicant submits that Groups I-IV are related to each other as different aspects of a single invention and that the interdependence of Groups I-IV as different aspects of a single invention is confirmed by virtue of the fact that 35 U.S.C. § 112 compels disclosure of all aspects of the invention in the one application which applicants have filed. In other words, a description of the means and method for using the genetically modified cell or non-human animal of Group I is a mandatory part of the application to the genetically modified cell or non-human animal itself. Indeed, if any of these aspects of a complete disclosure were omitted, the application could be considered defective under § 112, first paragraph. Finally, Applicant submits that a determination to make the pending group and species restriction requirement final must evidence the patentable distinctness of all defined groups and species, one from another.

This is not found persuasive because PCT Rule 13.2 clearly states that unity of invention between different categories of inventions will only be found to exist only if the following specific combinations of inventions are present:

1) A product and a special process of manufacture of said product.

2) A product and a process of use of said product.

3) A product, a special process of manufacture of said product, and a process of use of said product.

4) A process and an apparatus specially designed to carry out said process.

5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include a product and multiple methods of using said product, as claimed in the instant application (see MPEP § 1850). Item 2) clearly refers to one product and one method of using the product, and not to multiple methods of using the product. Therefore, Applicant's argument that Group I and Groups II-IV are related to each other as product and process of use (i.e., an allowed combination), is not found persuasive. With respect to the argument that the Examiner must demonstrate that the different groups and species are patentable distinct, it is noted that, in the restriction requirement mailed on 03/04/2008, the Examiner presented evidence as to why Groups I-IV and the different species are patentable distinct. It is also noted that Applicant did not address any of the arguments presented by the Examiner in the restriction requirement of 03/04/2008

However, since a search for the invention of Group I rendered results relevant for the inventions of Groups II and IV, **the restriction requirement between Groups I, II, and IV is hereby withdrawn.** In view of the above noted withdrawal of the restriction requirement, applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is

allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Similarly, since a search for the elected species rendered results relevant for the other species, the species election requirement is hereby withdrawn.

The requirement between the inventions of Groups I, II, IV and the invention of Group III is still deemed proper and is therefore made FINAL.

Claims 28 and 29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-27 and 30-47 are under examination.

Specification

2. The disclosure is objected to because it is unclear what the recitation of □□□˜□ means (see p. 71. line 16). Additionally, the disclosure is objected to because of the recitation of mice lacking "functional a functional Blimp-1 protein" (p. 68, lines 6 and 7).

Appropriate correction is required.

Claim Objections

3. Claims 17-19, 26, and 27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n).

4. Claim 30 is objected to because of the recitation of an agent which has the ability to "agonise" terminal differentiation. It is noted that "agonise" is the British variant of "agonize" (see Merriam-Webster dictionary). Appropriate correction to "indicative of the ability of the one or more agents to act as agonists or antagonists of terminal differentiation" is suggested.

5. Claim 18 is objected to because of the recitation of an organism provided in the form of "gametes or ES cells". It is noted that gametes and ES cells are cells and not organisms. Correction to the claim to recite "the genetic modified cells or non-human organism of any of the claims 1 to 14, 16, and 17, wherein the cells are gametes or ES cells and wherein the non-human organism is provided in the form of an embryo" is suggested.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites the limitation "genetic material" in 31. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112 - written description

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-6, 8-27, and 30-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶1"Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation

between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Claims 1-6, 8-27, and 30-47 are drawn to a modified cell comprising a modified *blimp* allele encoding full length Blimp or functional/non-functional parts, forms, homologues, or variants thereof, wherein the *blimp* allele is present in either homozygous or heterozygous form and wherein the presence of Blimp in the cell is associated with a commitment of the modified cell to differentiate (it is noted that the specification defines the non-functional parts, forms, homologues, or variants thereof as not being able to function as transcription factors, see p. 24, lines 28-30). Specifically at issue is the breadth to any functional part, form, homologue, or variant of Blimp in particular since, in order to be functional as claimed, the recited parts, forms, homologues, or variants must maintain Blimp transcriptional activity. Claims 1-6, 8-27, and 30-47 encompass a wide and variable genus of polypeptide the structure of which is not sufficiently disclosed in the specification and the claims.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude the inventors had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to

practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that the Applicants were in possession of the claimed invention (January 5, 2001, Fed. Reg., Vol. 66, No. 4, pp.1099-11). In analyzing whether the written description requirement is met for the genus claims, it is determined whether representative numbers of species have been described by their complete structure and functional characteristics.

When the claims are analyzed in light of the specification, the part, form, homolog, or variant can be any polypeptide as long as is able to maintain Blimp activity; thus, the claimed genus is very large and a great deal of variability is encompassed by the instant claims. With the exception of full length Blimp and a partial Blimp polypeptide which lacks the DNA-binding motif (i.e., a polypeptide which is functionally inactive), the specification fails to describe additional representative species of the polypeptides mentioned above. The specification discloses that the functional polypeptide is not particularly limited by its structure. For example, the part could be any epitope comprising less than 5 amino acids; the variant polypeptides include proteins derived from the wild type Blimp by deletions, addition, or substitution of one or more amino acids and could have 40% homology with the wild type Blimp (p. 22, lines 24-31, p. 23, lines 1-11 and 18-31). The genus of the polypeptides is described by its function as a transcription factor, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes,

of the different polypeptides. Applicant has not provided any information besides the characterization of the genus as having transcription factor activity. The specification only discloses that a predicted non-essential amino acid could be replaced with another amino acid from the same side chain family or that mutations can be randomly introduced along all or part of Blimp, followed by screening for functional mutants (p. 30, lines 9-15). This limited characterization, however, does not indicate that the Applicant had possession of the claimed genus of polypeptides. Applicant is relying upon biological activity and the disclosure of the wild type Blimp to support an entire genus. It is well known that minor structural differences among even structurally related compounds can result in substantially different biology. The specification fails to disclose what requirements a polypeptide must meet to have Blimp activity, i.e., the specification fails to provide the relationship between structure and function for the claimed polypeptides. Therefore, the specification fails to disclose what requirements a polypeptide must meet in order to have Blimp activity. The specification does not contain any disclosure of the structure of all variants. One skilled in the art would know that a change of even one amino acid residue in the claimed sequences could render an inactive protein or a protein with a different activity. Therefore, Applicant has not disclosed the requisite structural features of the polypeptide that would result in Blimp activity, a feature deemed essential for the instant invention. Therefore, one of skill in the art would not recognize Applicant to be in possession of the entire genus of functional parts, forms, homologues, or variants of Blimp.

In conclusion, this limited information is not sufficient to reasonably convey to

one of ordinary skills in the art that the Applicants invented what was claimed. Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 2, 6, 8, 10, 11, 17, 19-25, 31, 35, 44, 45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Chang et al. (Nat. Immunol., 2000, 1: 169-176, Applicant's IDS).

Chang et al. teach modified U937 cells (i.e., a human macrophage precursors) comprising a modified *blimp* gene encoding a fusion protein between wild type Blimp and GFP, wherein the modified cell is obtained by using a bicistronic retroviral vector encoding wild type Blimp fused to GFP, wherein the presence of Blimp within the cells is monitored via GFP expression, and wherein Blimp expression results in terminal differentiation of U937 cells to macrophages (claims 1, 2, 6, 8, 10, 11, 19, 31, 35, 44, 45, and 47) (p. 172, column 1). Chang et al. teach using GFP expression to monitor and isolate the differentiated macrophages by flow cytometry by using both GFP and CD11 as selection markers, i.e., Chang et al. teach isolating cells exhibiting reporter activity from cells not exhibiting reporter activity (claims 20-25) (p. 172, column 1 and p.

173, Fig. 5). Since Chang et al. teach all the claim limitations, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-27 and 30-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glimacher et al. (PGPUB 2002/0059652), in view of both Shaffer et al. (Immunity, 2002, 17: 51-62) and Mountford et al. (Proc. Natl. Acad. Sci. USA, 1994, 91: 4303-4307, Applicant's IDS).

Glimacher et al. teach a method of *in vitro* or *in vivo* screening for agonists or antagonists of terminal differentiation of B- or T-cells, the method comprising contacting genetically a test compound with genetically modified B- or T-cells or transgenic mice comprising genetically modified B- or T-cells, wherein the modified B- or T-cells comprise a modified *xbp-1* gene encoding functional or non-functional XBP-1 polypeptide co-expressed with a selectable marker or GFP; the transgenic mice are obtained by genetically modifying mouse embryonic stem cells (ES) and the genetically modified cells could be either homozygous or heterozygous for the modified *xbp-1* gene (claims 1, 2, 4-12, 18, 19, 30, 31, 33-41) (Abstract, p. 1, paragraphs 0004 and 0006, p. 2, paragraph 0011, p. 4, paragraph 0031, p. 5, paragraph 0053, p. 7, paragraphs 0068

and 0073, p. 9, paragraphs 0082 and 0083, p. 10, paragraph 0091, p. 21, paragraph 0178, p. 24, paragraph 0214). Glimacher et al. teach that their genetically modified B- or T-cells are ASC and $CD4^+$cells, respectively (claims 13, 14, 16, 26, 27, 42, and 43) (p. 3, paragraph 0019, p. 5, paragraph 0042, p. 10, paragraph 0091). Glimacher et al. also teach selecting their genetically modified and terminally differentiated cells by flow cytometry based on GFP, CD44, and syndecan-1 expression, i.e., they teach a method of phenotyping and monitoring a cell of the hematopoietic system by detecting reporter activity and using further selection markers wherein GFP detection is indicative of terminal differentiation and a substantially purified population of ASC obtained via such a method (claims15, 17 and 20-25) (p. 24, paragraph 0214).

Glimacher et al. do not teach genetically altering the *blimp* gene (claims 1-27 and 30-47). However, they do teach that the XBP-1 transcription factor acts downstream of Blimp (p.24-25, paragraphs 0214 and 0215). Additionally, Shaffer et al. also teach that Blimp-1 is the master regulator of plasma cells terminal differentiation, wherein Blimp acts by allowing the expression of specific transcription factors such as XBP-1 (Abstract, p. 56, Fig. 3, p. 59, Fig. 7, p. 60, column 1, last paragraph, column 2). Based on these teachings, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the cells and methods of Glimacher et al. by substituting their XBP-1 with Blimp to achieve the predictable result of obtaining cells suitable to be used in a method of screening for agonists or antagonists of terminal differentiation of B- or T-cells. It is noted that, by doing so, one of skill in the art would have necessarily

used a targeting vector comprising a modified *blimp* gene as recited in claims 44, 45, and 47.

Although Glimacher et al. and Shaffer et al. teach homologous recombination at the *blimp* locus, they do not specifically teach insertion within an intron of a *blimp* allele (claims 3, 32, and 46). However, at the time the invention was made, homologous recombination wherein insertion can take place in coding or non-coding regions of a gene according to the needs was taught by the prior art (see Mountford et al. teach insertion in both coding and Abstract, p. 4303, column 2 and Fig. 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the cells and method of Glimacher et al. and Shaffer et al. by inserting their construct within an intron of the *blimp* gene to achieve the predictable result of obtaining genetically modified cells to be used in a screening method for agents which could modulate the terminal differentiation of B- or T-cells.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

14. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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